The impact of spacer modifications on 5-HT$_{1A}$/5-HT$_7$ receptor selectivity in the group of arylpiperazine ligands

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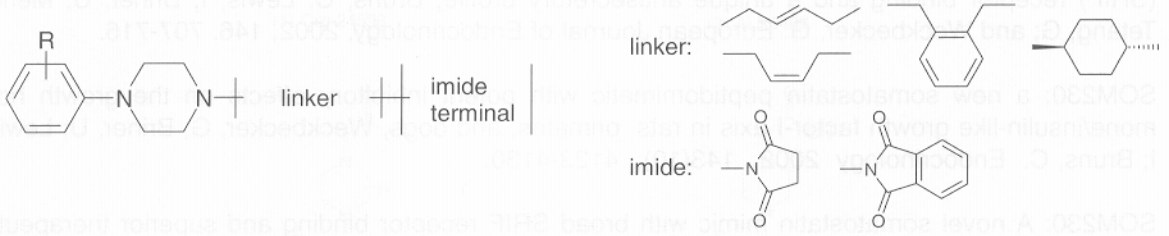
A serotonin 5-HT$_7$ receptor subtype was identified in 1993, and a number of previously described selective 5-HT ligands (e.g. 5-CT, 8-OH-DPAT, ritanserin) were found to be potent 5-HT$_7$ agents. Particularly, close similarities between the binding sites for both 5-HT$_{1A}$ and 5-HT$_7$ receptors were reported; in consequence, it was shown that 5-HT$_{1A}$ receptor ligands of the arylpiperazine type often displayed additional 5-HT$_7$ activity. The same was also observed after screening our compound library for 5-HT$_7$ receptor affinity, and compounds showing distinct potency at those binding sites were identified among *ortho*-methoxyphenylpiperazine (oMPP) derivatives. Hence identification of the structural features responsible for discrimination between these two receptor subtypes is an important issue in designing new selective ligands.

Being a basic element of the structure of long-chain arylpiperazines (LCAPs), the flexible aliphatic spacer determines a high conformational freedom and may allows their efficient fitting into the binding sites of different receptors.

In order to establish the impact of spacer modifications on 5-HT$_{1A}$/5-HT$_7$ selectivity, a series of NAN190 and MM77 analogues were designed and synthesized.



Conformationally constrained derivatives were obtained by replacing the methylene chain with *cis*- and *trans*-2-butene, 1,2-bis-methylbenzene, or 1e,4e-cyclohexane fragments. The flexible and *trans*-2-butene derivatives showed the highest *in vitro* activity for both the receptors tested. Of all the modifications applied, introduction of a cyclohexane ring maintaining high 5-HT$_{1A}$ receptor affinity significantly decreased the 5-HT$_7$ binding.

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